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Does COVID-19 Infection Pose a Risk to Women of Childbearing Age?

COVID-19 Enfeksiyonu Doğurganlık Çağındaki Kadınlar için Risk Oluşturur mu?

Kazım KIRATLI [1*], Mustafa SENGUL [2]

[1] Katip Celebi University Ataturk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey
[2] Katip Celebi University Ataturk Training and Research Hospital, Department of Gynecology and Obstetrics, Izmir, Turkey

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Abstract

Objective: This study aims to investigate the potential differential impact of COVID-19 infection on pregnant women compared to non-pregnant individuals of childbearing age by evaluating laboratory findings from both inpatient and outpatient cases.

Material and Methods: From the onset of COVID-19 in Turkey in March 2020 until the commencement of vaccination, a total of 94 COVID-19 patients were included in three separate groups: pregnant women and non-pregnant individuals with COVID-19 (with and without pneumonia). Sociodemographic data and examination findings were retrospectively retrieved from the hospital information system.

Results: The study revealed that pregnant women, with a mean age of 28.87±1.38, experienced a significantly shorter mean length of hospital stay of 5.03±0.49 days compared to the other groups ($p<0.001$). Notably, pregnant women exhibited significant variations in urea, creatinine, white blood cell count, neutrophil count, hemoglobin, and hematocrit values in comparison to the other groups ($p<0.001$). Moreover, there were significant differences among the three groups concerning neutrophil and lymphocyte percentage values ($p<0.001$).

Conclusion: The study suggests that COVID-19 infection in pregnant women is associated with more favorable clinical outcomes, shorter length of hospital stay, and relatively moderate alterations in laboratory findings when accounting for pregnancy-induced changes. It is implied that pregnancy might not pose as substantial a risk factor for severe COVID-19 infection as advanced age or underlying chronic conditions such as diabetes, asthma, COPD, and malignancy.

Keywords: COVID-19; Infection; Pregnancy; Pneumonia

Özet

Amaç: Bu çalışma, hem yatan hem de ayakta tedavi vakalarından elde edilen laboratuvar bulgularını değerlendirerek, çocuk doğurma çağındaki hamile olmayan bireylerle karşılaştırıldığında, COVID-19 enfeksiyonunun hamile kadınlar üzerindeki potansiyel farklı etkisini araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Türkiye'de COVID-19'un ortaya çıktığı Mart 2020'den aşılamanın başlamasına kadar toplam 94 COVID-19 hastası üç ayrı gruba dahil edildi: hamile kadınlar ve hamile olmayan COVID-19'lu bireyler (pnömonisi olan ve olmayanlar) . Sosyodemografik veriler ve muayene bulguları hastane bilgi sisteminden geriye dönük olarak elde edildi.

Bulgular: Araştırmada yaş ortalaması 28,87±1,38 olan gebelerin diğer gruplara göre anlamlı olarak daha kısa ortalama hastanede kalış süresi (5,03±0,49 gün) yaşadığı ortaya çıktı ($p<0,001$). Özellikle gebelerde üre, kreatinin, beyaz küre sayısı, nötrofil sayısı, hemoglobin ve hematokrit değerlerinde diğer gruplara göre anlamlı farklılıklar görüldü ($p<0,001$). Ayrıca nötrofil ve lenfosit yüzde değerleri açısından da üç grup arasında anlamlı fark vardı ($p<0,001$).

Sonuç: Çalışma, hamile kadınlarda COVID-19 enfeksiyonunun, hamileliğin neden olduğu değişiklikler hesaba katıldığında daha olumlu klinik sonuçlar, daha kısa hastanede kalış süresi ve laboratuvar bulgularında nispeten orta düzeyde değişikliklerle ilişkili olduğunu öne sürüyor. Gebeliğin ciddi COVID-19 enfeksiyonu açısından ileri yaş veya diyabet, astım, KOAH ve malignite gibi altta yatan kronik durumlar kadar önemli bir risk faktörü oluşturmayabileceği düşünülmektedir.

Anahtar Kelimeler: Covid-19, Enfeksiyon, Gebelik, Pnömoni

***Sorumlu Yazar/Corresponding Author:** Kazım KIRATLI, Katip Celebi University Ataturk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey. **E-mail:** drkazimkiratli@gmail.com

INTRODUCTION

The emergence of the COVID-19 pandemic can be traced back to December 29, 2019, when four cases of pneumonia with an unidentified origin were identified in Wuhan, the capital of China's Hubei province. Subsequent whole genome sequencing of the oropharynx and nasal samples from these cases on January 12, 2020, revealed the presence of a previously undiscovered coronavirus (CoV) strain. On February 11, 2020, the International Committee on Virus Taxonomy named it "Severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2), and the World Health Organization (WHO) designated the resulting disease as COVID-19 [1]. SARS-CoV-2 is primarily transmitted through inhalation of droplets expelled into the environment by infected individuals through coughing or sneezing. Alternatively, transmission can occur by touching contaminated surfaces and subsequently introducing the virus into the body through the mouth or nose [2,3]. The genetic similarity of SARS-CoV-2 to other coronaviruses such as severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) (79%) and Middle East respiratory syndrome coronavirus (MERS) (50%) places it within the same group. Coronaviruses, a class of enveloped, positive single-stranded RNA viruses, can present with a spectrum of illnesses, spanning from common cold symptoms to severe pneumonia and fatality [4].

Upon entering a host, SARS-CoV-2 initially attaches to cell receptors and gains entry by means of fusion. Following this, the viral RNA penetrates the cell nucleus for replication, utilizing viral mRNA to synthesize viral proteins in a process known as biosynthesis. Subsequently, newly formed viral particles are enclosed in vesicles, transported to the cell membrane, and eventually released [5,6].

A notable observation is the heightened expression and activity of angiotensin-converting enzyme 2 (ACE-2), a key receptor for SARS-CoV-2, in the uterus, kidney, and placenta during pregnancy. Consequently, these reproductive organs are considered prime targets for SARS-CoV-2 infection [7]. The severity of symptoms, such as hypoxia and pneumonia, is thought to be correlated with increased ACE-2 expression [8]. Transmembrane ACE-2 enzymes are also found in various other tissues, including enterocytes, type II alveolar cells, smooth muscles, vascular endothelial tissue, and certain neurons [9].

Pregnant women faced high mortality rates during past significant pandemics such as the 1918 Spanish influenza (27-50% mortality), SARS-CoV-1 (25-30% mortality), and MERS (~40% mortality) [2,3]. In the more recent H1N1 pandemic, pregnant and perinatal mortality rates

surpassed those of the general population [10]. There is a growing body of evidence suggesting that complications like miscarriage, intrauterine and neonatal deaths, preterm births, and preeclampsia are on the rise with the spread of COVID-19 [11]. Pregnancy-related immunological and physiological changes, including increased oxygen demand, shifts in T lymphocyte immunity, and decreased functional residual capacity, render pregnant individuals more vulnerable to respiratory pathogens, leading to elevated maternal and fetal risks [12]. Irrespective of pregnancy, COVID-19 exhibits a more severe course in the elderly (above 65 years old) and individuals with underlying chronic conditions like diabetes, obesity, kidney disease, heart disease, lung disease, and cancer, independent of age [13]. Studies investigating laboratory findings among COVID-19 patients have reported changes in parameters such as whole blood composition, liver enzymes, albumin, creatine kinase (CK), ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and D-dimer levels [14].

Given the swift global spread of COVID-19, its recent discovery, the absence of definitive treatment, and the historical vulnerability of pregnant women in pandemics, concerns for pregnant women and fetuses have intensified. The aim of this study was to meticulously assess clinical and laboratory data from both pregnant and non-pregnant female patients with COVID-19 who were monitored as both inpatients and outpatients, as well as to discern whether the disease's impact on pregnancy differs from its effects on non-pregnant individuals.

METHODS

In our study, a total of 94 COVID-19 patients were divided into 3 separate groups and analyzed: 1st group: 31 patients (pregnant women), 2nd group: 30 patients (non-pregnant, pneumonia +), 3rd group: 33 patients (non-pregnant, pneumonia -). The non-pregnant patients consisted of women of reproductive age. The study's first group consisted of all pregnant cases (31 patients) who underwent follow-up at our clinic between March 2020, when Turkey's Covid-19 outbreak began, and January 2021, when the nation's first vaccination program was implemented. The patients in the other two non-pregnant groups were drawn at random and similar numbers from patients of reproductive age who were under treatment for the same period of time. Individuals with any comorbidities that may affect the course of Covid-19 are not present in the study groups. This research was planned retrospectively, sociodemographic characteristics, clinical manifestations, and findings from examinations and imaging studies were extracted from the hospital information management system.

To identify and isolate individuals infected with SARS-CoV-2, we employed PCR testing utilizing the Bio-speedy SARS-Cov-2 real-time polymerase chain reaction (Rt-PCR) detection kit developed by Bioksen in Istanbul, Turkey. This diagnostic procedure was performed on samples collected from nasopharyngeal swabs obtained from the patients.

Ethical Approval

The research was approved by the Ministry of Health for Scientific Research and Izmir Katip Celebi University (İKCÜ) Ethics Committee (Ministry of Health Scientific Research Form No: 2021-04-18T17_42_00) (İKCÜ Non-Invasive Clinical Research Ethics Committee Decision Form: 0244/29.04.2021).

Statistical Analysis

The statistical analysis of the study data was conducted using the SPSS version 21.0 (Statistical Package for the Social Sciences) software. The normality of continuous variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For group comparisons, the ANOVA test with post hoc Bonferroni correction was employed for continuous variables conforming to normal distribution, while the Kruskal-Wallis test was utilized for continuous variables not conforming to normal distribution. All measurements are presented as "mean ± standard error." A significance level of $p<0.05$ was considered as the threshold for significance.

RESULTS

The mean age of the pregnant women included in the study was 28.87±1.38 years. Their mean length of hospital stay was 5.03±0.49 days, which significantly differed from the other groups ($p<0.001$) (Table 1). Pregnant and non-pregnant adult patients exhibited similar rates of COVID-19 symptoms. The most common symptom in both groups was fever (pregnant: 73.3%; non-pregnant: 71.6%), followed by cough (pregnant: 53.3%; non-pregnant: 63.3%), and headache (pregnant: 43.3%; non-pregnant: 46.6%). Additional common symptoms included myalgia (30%) and chills (26.6%) in pregnant women, as well as a reduced sense of taste/smell (35%) and fatigue (26.6%) in non-pregnant patients. Other frequent symptoms are detailed in Table 2.

Significant differences were observed between pregnant women and the other groups concerning urea and creatinine values ($p<0.001$). Furthermore, LDH values were notably higher in the pneumonia group compared to the other two groups ($p<0.001$). Pregnant patients and those with pneumonia displayed elevated CRP, ferritin, ESR, and D-dimer values (Table 1).

Table 1- Length of Hospital Stay, Mean Age and Biochemical Parameters of the Patients

Parameters	Pregnant patients	Non-Pregnant Pneumonia (+)	Non-Pregnant Pneumonia (-)	p
Age	28.87±1.38[a*]	36.79±1.30[b]	33.57±1.43[b]	<0.001
Hospitalization Period (day)	5.03±0.49[a]	10.17±0.65[b]	9.31±0.59[b]	<0.001
Ure	6.87±0.43[a]	9.76±0.51[b]	9.46±0.42[b]	<0.001
Creatinine	0.60±0.02[a]	0.74±0.02[b]	0.69±0.01[b]	<0.001
AST	22.37±2.36[a]	28.03±3.57[a]	21.51±3.06[a]	0.272
ALT	18.86±3.77[a]	38.20±9.40[a]	25.59±6.82[a]	0.162
LDH	168.20±11.64[a]	219.10±13.67[b]	147.03±7.77[a]	<0.001
CK	84.13±8.50[a]	74.00±12.81[a]	79.29±8.60[a]	0.785
CRP	25.53±5.79[ab]	49.67±13.69[b]	9.43±4.41[a]	0.005
D-dimer	1025.67±322.94[a]	542.52±212.52[ab]	157.31±21.86[b]	0.016
Ferritin	83.97±10.52[ab]	141.83±27.62[b]	60.49±14.53[a]	0.008
Procalcitonin	0.08±0.01[a]	0.10±0.03[a]	0.11±0.08[a]	0.930
ESR	30.97±4.59[a]	36.03±3.90[a]	15.63±2.64[b]	<0.001

* Different letters indicate statistical significance.

Table 2- Distribution of Symptoms

Symptoms	Pregnants	Non- pregnants
Fever	%73.3	%71.6
Cough	%53.3	%63.3
Headache	%43.3	%46.6
Myalgia	%30	%23.3
Chills	%26.6	%21.6
Loss of taste/smell	%23.3	%35
Fatigue/Weakness	%20	%26.6
Dyspnea	%16.6	%25
Nausea/Vomiting	%13.3	%16.6
Sore throat/runny nose	%6.6	%8.3
Diarrhea	%3.3	%3.3

In terms of WBC count, neutrophil count, hemoglobin, and hematocrit values, there were significant differences between pregnant women and the other groups ($p<0.001$). Moreover, significant differences emerged among the three groups in terms of neutrophil and lymphocyte percentage values ($p<0.001$), while no differences were observed between the three groups concerning lymphocyte and platelet counts ($p>0.05$) (Table 3).

Table 3- Complete Blood Parameters of the Patients

Parameters	Pregnant patients	Non-Pregnant Pneumonia (+)	Non-Pregnant Pneumonia (-)	p
WBC	10.43 ± 0.56^{a}	6.62 ± 0.73^{b}	5.79 ± 0.55^{b}	<0.001
NEU	7.93 ± 0.52^{a}	4.52 ± 0.72^{b}	3.41 ± 0.47^{b}	<0.001
NEU %	74.58 ± 1.51^{a}	64.74 ± 1.90^{b}	53.23 ± 2.47^{c}	<0.001
LYM	1.77 ± 0.10^{a}	1.52 ± 0.10^{a}	1.72 ± 0.09^{a}	0.178
LYM %	18.02 ± 1.20^{a}	26.05 ± 1.84^{b}	34.77 ± 2.14^{c}	<0.001

MONO	0.63±0.03[a]	0.48±0.04[a]	0.57±0.06[a]	0.078
MONO %	6.44±0.47[a]	7.78±0.54[a]	10.02±0.61[b]	<0.001
RBC	3.94±0.08[a]	4.58±0.08[b]	4.56±0.07[b]	<0.001
HGB	11.28±0.25[a]	12.54±0.29[b]	12.65±0.23[b]	<0.001
HCT	32.89±0.58[a]	37.87±0.66[b]	38.15±0.53[b]	<0.001
PDW	12.64±0.56[a]	11.98±0.34[a]	12.35±0.34[a]	0.555
RDW	14.14±0.59[a]	13.64±0.29[a]	13.59±0.29[a]	0.583
PLT	230.90±14.06[a]	252.41±15.42[a]	237.17±12.43[a]	0.551
PCT	0.26±0.02[a]	0.26±0.01[a]	0.25±0.01[a]	0.840

* Different letters indicate statistical significance.

The analysis of obstetric characteristics revealed that the highest number of pregnancies (gravida) was 2 (46.7% - n:14), with the maximum parity number being 1 (56.7% - n:17). The cesarean delivery rate was 56.7% (n:17), and the rate of premature births (<37 weeks) stood at 26.7% (n:8). The mean fetal weight was recorded as 3048 g (Table 4).

Table 4- Obstetrical Characteristics

Gravida	Parity	Birth week	Fetal growth retardation (<2500 g)	Type of birth (Cesarean section)	Mean fetus weight (g)	Mean postpartum Hgb (After 6 hours)
1.9±0.9 (1-5)	1.0±0.8 (0-4)	38.2±1.8 (35-40)	%26.7 (n:8)	%56.7 (n:17)	3048.3±472.2 (2040-4250)	10.1±1.5 (7.6-13.5)

DISCUSSION

Physiological changes inherent to pregnancy, such as a reduction in anticoagulant factors coupled with an elevation in procoagulant factors, result in a hypercoagulable state, leading to an increase in D-dimer levels [15]. Concurrently, adverse outcomes like preterm labor, low birth weight infants, decreased Apgar scores, and occurrences of preeclampsia/eclampsia are more prevalent among pregnant women with pneumonia [16]. Coagulation disturbances noted in COVID-19 non-pregnant patients are linked to poorer

prognoses, prompting concerns that the pre-existing pregnancy-related coagulopathy could amplify the morbidity and mortality associated with COVID-19 [17].

Among the general population, the most common COVID-19 symptoms include cough, fever, myalgia, fatigue, headache, and shortness of breath, respectively [18]. Pregnant women similarly experience SARS-CoV-2 symptoms, with fever and cough being predominant, and the severity parallels that in non-pregnant counterparts [19-21]. In our study, comparable rates of fever, cough, and headache were the most prevalent symptoms in both groups.

A comprehensive meta-analysis involving 26 studies (including 11,580 women) focused on pregnant individuals with suspected or confirmed COVID-19 infection. This analysis revealed that a severe form of the disease was observed in 6-21% of patients (mean 13%), with 2-7% requiring intensive care unit (ICU) admission (mean 4%), 1-5% needing mechanical ventilation (mean 3%), and 0.4% necessitating extracorporeal membrane oxygenation. Concurrent maternal comorbidities such as chronic hypertension, advancing maternal age, high body mass index, and diabetes were identified as risk factors for a severe disease course [22]. A Chinese study of hospitalized pregnant women with COVID-19 reported that 77% experienced fever and 23% exhibited shortness of breath. Within this cohort, 46% delivered prematurely between weeks 32-36 of gestation. Remarkably, 23% responded positively to treatment and were discharged to resume their pregnancies. Severe pneumonia and multi-organ dysfunction requiring ICU care and extracorporeal membrane oxygenation were noted in 7.6% of cases [23]. Another meta-analysis confirmed that pregnant women with COVID-19 manifested similar symptoms and experienced comparable disease severity as the broader adult population [24]. A study on pregnant women with COVID-19 pneumonia highlighted that the ICU admission rate resembled that of non-pregnant women. However, rates of preterm labor and cesarean delivery were higher compared to pregnant women without COVID-19 [25]. In our study, the cesarean section rate reached 56.7%, while preterm delivery and low birth weight incidence were found as 26.7%.

In a study by Liu et al. [26], 85% of patients exhibited elevated LDH and CRP levels, while 15% had leukocytosis and 43% experienced lymphopenia. Neutrophil counts were elevated in 57% of cases, whereas platelet counts remained within the normal range for all patients. Furthermore, 85%, 72%, and 85% of patients showed normal procalcitonin, ALT, and AST levels, respectively. However, low albumin levels were noted in 43% of patients. Another study reported a higher prevalence of leukocytosis and elevated neutrophil ratios in pregnant individuals infected with COVID-19. Nonetheless, no notable difference emerged between

pregnant and non-pregnant groups in terms of lymphopenia. Elevated CRP levels were consistently observed in a majority of cases [27]. In a larger study including COVID-19 patients, common laboratory findings encompassed increased CRP (73.6%), decreased albumin (62.9%), elevated ESR (61.2%), decreased eosinophil counts (58.4%), lymphopenia (47.9%), and increased LDH levels (46.2%) [28]. Xie et al. [29] identified lymphopenia, leukopenia, elevated CRP, ferritin, and LDH as prominent laboratory findings among COVID-19 patients. Similarly, in another study on pregnant women, the most frequent laboratory findings were increased neutrophil counts, lymphopenia, and elevated CRP values. While the rate of leukocytosis and thrombocytopenia was higher in pregnant women, the percentage of elevated CRP was lower compared to non-pregnant individuals. D-dimer levels were elevated in both groups, but notably higher in pregnant women. Lymphopenia and elevated CRP were recurrent findings in meta-analyses of other pregnant patients [20]. In our study, LDH values were elevated in the pneumonia group compared to the other two groups, while CRP, ferritin, D-dimer, and ESR values were higher in pregnant patients and those with pneumonia. Notably, significant neutropenia was observed in non-pregnant patients, and hemoglobin levels were lower in pregnant patients. Thrombocytopenia and lymphopenia displayed similar patterns between the groups.

In another study focused on pregnant women, the results revealed that markers such as neutrophils, WBC count, procalcitonin, CRP, and D-dimer were notably elevated in pregnant individuals. Additionally, the mean lymphocyte percentage was lower compared to non-pregnant women [30].

It is important to acknowledge several limitations in our study. The exclusive inclusion of pregnant women in their last trimester might not comprehensively capture the virus's impact during the 1st and 2nd trimesters. Moreover, the study does not provide insight into the long-term effects on both pregnant women and fetuses. The study's relatively small sample size and the fact that it was conducted before vaccination are additional limitations that need to be considered. Although the higher average age of nonpregnant women in each group may be considered a limitation, randomization may also suggest that nonpregnant women of childbearing age may be reluctant to seek medical care when they first show symptoms.

CONCLUSION

This study attempted to elucidate the trajectory of COVID-19 in pregnant patients compared to the non-pregnant adult population. Given past experiences with severe respiratory illnesses,

initial assumptions suggested that SARS-CoV-2 might disproportionately impact pregnant women. However, the majority of data point to relatively lower rates of maternal morbidity and mortality in comparison to prior coronavirus pandemics. The study revealed a more favorable disease course among pregnant women, characterized by shorter length of hospital stay and moderate alterations in laboratory parameters (taking pregnancy-related changes into account). These results indicate that, when considering factors like age and underlying health conditions, pregnancy might not pose as a serious risk for COVID-19 as advanced age or chronic illnesses such as diabetes, asthma, COPD, and malignancy. Considering the known associations between being female and younger age with improved COVID-19 outcomes, it is likely that this group would exhibit lower morbidity and mortality rates within the general population. However, the observation of increased rates of low birth weight, cesarean section, and preterm births in pregnant women with COVID-19 raises concerns about potential correlations between the disease and pregnancy complications. While our study provides valuable insights, the long-term effects of COVID-19 on fetuses and newborns remain uncertain. Further studies are needed for enhancing our understanding of pregnancy management during illness.

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Authorship Contributions: Concept – KK, MS; Design – KK, MS; Data Collection and/or Processing – KK, MS; Analysis and/or Interpretation – KK, MS; Literature Review – KK, MS; Writing – KK.

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